

This Month in *AJP*

Frequent p53 Mutations in Normal Human Skin

Human skin contains apparently normal keratinocytes which are immunoreactive for p53. More than 50% of keratinocyte clusters staining for p53 have mutations in the gene. However, p53 clones and cancers, which may develop in areas adjacent to the clusters, do not share the same mutation. Thus, there is no direct proof that p53 mutations are genetically linked to skin tumors. Nevertheless, it is known that a single dose of ultraviolet radiation (UVA or UVB) and γ radiation, well known carcinogenic agents for the skin, induce p53 expression. Ling et al (*Am J Pathol* 2001, 159:1247–1253) analyzed keratinocytes from sun-exposed skin and shielded skin (skin from the same individual covered with denim fabric) from one individual as well as shielded skin from two additional volunteers. The authors obtained skin biopsies and then isolated single keratinocytes by laser capture microdissection. The authors identified 14 different p53 mutations in 26 of 99 keratinocytes from which the p53 gene could be amplified for analysis. Mutations were also detected in biopsies of shielded skin and the mutations persisted for at least two months despite protection against the sun. The authors hypothesize that p53 mutations in terminally differentiated cells may occur in normal skin but probably do not persist. However, p53 mutations in stem cells may have a role in the initiation of skin carcinogenesis.

Specificity and Similarities of Gene Expression Patterns among Adenocarcinomas of Lung, Colon, and Ovary

An important goal of analysis of gene expression in human tumors using microarray methodology is to develop a molecular classification of tumors. It is not known at the moment whether a molecular classification would differ significantly from morphological classifications currently in use. Nevertheless, molecular analysis may identify subsets of tumors with different metastatic potential and sensitivity to therapy which are undistinguishable by conventional criteria. To achieve a reliable molecular classification, it is first necessary to know whether tumors of similar histology developing in different organs have gene expression profiles that are specific for each site. Giordano et al (*Am J Pathol* 2001, 159:1231–1238) studied the expression of 6800 genes in 57 lung, 51 colon, and 46 ovarian primary adenocarcinomas. Genes expressed at high average levels as well as those expressed at low average levels could be distinguished for each set of tumors. Although there was heterogeneity in patterns of gene expression for each individual tumor regardless of site, approximately 30 genes had expression patterns which were specific for the organ site of the adenocarcinoma. Using a set of ten specific genes, 152 of 154 tumors were correctly classified as to organ site. Two outliers, one colon tumor and one from the ovary, proved to be a gastrointestinal stromal tumor (GIST) and a metastatic tumor, respectively. Based on these studies it is now possible to extend the approach to the analysis of large sets of tumor types. Depending on the information generated by future studies, the results may have profound impact on the practice of pathology.

Distinct Genetic Pathways in Juvenile Polyposis Syndrome

Juvenile polyposis (JPS) is a rare disease characterized by the presence of hamartomatous polyps in the gastrointestinal tract and increased risk of GI malignancy. It is known that a subset of JPS cases, between 20 to 50%, are caused by genetic alterations in the SMAD4 gene, a component of the TGF- β signaling pathway. Woodford-Richens et al (*Am J Pathol* 2001, 159:1293–1300) made a comprehensive survey of germline SMAD4 mutations in a cohort of JPS patients and analyzed the polyps of these patients for SMAD4 protein expression. Almost all SMAD4 germline mutations could be detected by PCR analysis of genomic DNA. The authors found two distinct origins for the polyps. Those involving SMAD4 mutations resulting in loss of expression of the protein in the polyps and another in which SMAD4 involvement could be definitively excluded. The polyps originated by these distinct pathways also showed morphological differences.

Repopulation of the Liver with Fetal Cells

Repopulation of damaged livers by cell transplantation has recently been used as a system in which to study the proliferative capacity of hepatocytes and of liver cells with stem cell properties. Injured livers can be repopulated by transplantation of hepatocytes isolated from livers of adult rodents. Sandhu et al (*Am J Pathol* 2001, 159:1323–1334) investigated the capacity of rat fetal liver epithelial cells to form colonies in normal adult rat livers and to repopulate livers of rats treated with retrorsine. Sandhu et al obtained cells at day 14 of rat embryonic development (E14) and found that these cells could replace 5 to 10% of hepatocytes in normal livers approximately 6 months after transplantation. In

retorsine-injured liver, transplanted E14 cells replaced 60 to 80% of the parenchyma and formed multilobular structures containing both hepatocytes and bile duct cells (the transplanted cells were recognized by the expression of the marker enzyme dipeptidylpeptidase IV). Transplanted E14 cells continue to proliferate beyond 6 months after transplantation and differentiated into hepatocytes when engrafted into the liver parenchyma and into bile duct cells when located in the vicinity of host bile ducts. This study demonstrated that fetal liver epithelial cells are highly proliferative and can function as biopotential stem cells that generate both hepatocytes and biliary cells.

Mitochondrial Defects in a Disease Caused by Deficient Biosynthesis of Peroxisomes (Zellweger Syndrome)

The cerebro-hepato-renal syndrome known as Zellweger syndrome is the most severe form of the disorders of peroxisome biogenesis, causing early death in the affected children. Knockout mice deficient for the PEX56 gene serve as a good animal model for the human syndrome. Baumgart et al (*Am J Pathol* 2001, 159:1477–1494) report that the absence of functional peroxisomes leads to the proliferation of abnormal mitochondria with ultrastructural alterations and were detected in liver, kidney proximal tubules, adrenal cortex, heart, and other tissues and were associated with a marked increase in mitochondrial manganese-superoxide dismutase (MnSOD) detectable by both immunohistochemistry and *in situ* hybridization. The authors propose that there is an increased production of reactive oxygen species (ROS) in the altered mitochondria (probably induced by accumulation of lipid intermediates of peroxisomal β -oxidation) which may be important in the pathogenesis of multiple organ dysfunction in Zellweger syndrome.

Induction of Aortic Aneurysms by Urokinase-Type Plasminogen Activator (uPA)

Chronic infusion of angiotensin II causes abdominal aortic aneurysms in apolipoprotein E-deficient mice. Mice treated with angiotensin II develop a localized expansion of the suprarenal aorta, involving an approximate 75% increase in outer diameter accompanied by blood pressure elevation. Wang et al (*Am J Pathol* 2001, 159:1455–1464) report that the dilated aortic segment of the mouse aneurysm has similarities with human aortic aneurysms that include fragmentation of elastin, macrophage infiltration, and intravascular hemorrhage. Because uPA expression is increased in human abdominal aortic aneurysms, Wang et al determined whether similar increases would be present in angiotensin II-injected mice. They detected an approximately 13-fold increase in uPA expression in the aortic aneurysm segment, starting several days before aortic expansion. In contrast, uPA expression changed by about two-fold in the aortic arch, an area in which aneurysms do not develop in this experimental system. The results suggest that uPA may have a causal role in the pathogenesis of abdominal aortic aneurysms.